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Kandiah Jeyaseelan

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EXAMINER

GUDIBANDE, SATYANARAYAN R

ART UNIT

PAPER NUMBER

1654

NOTIFICATION DATE

DELIVERY MODE

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ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No. 10/559,649	Applicant(s) JEYASEELAN ET AL.	
	Examiner SATYANARAYANA R. GUDIBANDE	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 December 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 41-78 is/are pending in the application.
- 4a) Of the above claim(s) 41-54 and 68-78 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 55-67 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>12/12/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group II (claims 55-68) and election of SEQ ID NO: 3 a peptide species, election of reducing the serum cholesterol as the function of the peptide and election of oral administration as the method of administration in the reply filed on 4/21/08 and in a supplemental response on 4/25/08 is acknowledged. The traversal arguments were answered in the non-final action mailed 7/24/08.

Applicants continue to traverse the restriction requirement mailed 3/19/08 and the answer to traversal arguments made in the office action dated 7/24/08. Applicants wish to state on the record that they disagree with the Office's reasoning that "[T]he Zhu et al., reference discloses on page 754, section 3.3, that BmTXLP2 is an acidic protein composed of 78 residues containing 8 Cys residues which presumably form 4 disulphide bonds (emphasis added). The reference further provides on page 750, section 2.3, that prediction of signal sequences of precursor proteins was performed using SignallP. Thus, the protein sequence of Bm TXLP2 was based simply on direct translation of the nucleotide sequence, and using bioinformatics Zhu et al. predicted that BmTXLP2 protein is a sodium ion channel toxin. There is no mention of the isolation of peptide in the reference and the sequence of Fig. 1(b) was obtained by mere deduction using bioinformatics based on DNA cloning".

The arguments are not persuasive. These arguments have been considered before and it has been made clear that are not persuasive in the office action dated 7/24/08 (see pages 3 and 4). The rebuttal arguments presented clearly establishes the fact the BmTXLP2 peptide was in fact

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characterized using molecular cloning techniques (page 750, column 1, paragraph 1 of Zhu reference).

Applicant's amendment to claims in the response filed on 12/12/08 has been acknowledged.

Claims 44-78 are pending.

Claims 41-54 and 69-78 have been withdrawn from further consideration as being drawn to non-elected invention.

Claims 55-68 have been examined on the merit.

A search for the elected species SEQ ID NO: 3 indicated that it is not free of prior art. The art found has been applied in the rejection below.

Any objections and/or rejections made in the office action dated 7/24/08 and not specifically mentioned here are considered withdrawn.

Withdrawn Objections/Rejections

Claim Objections

Applicant's arguments, see page 15, paragraph 1, filed 12/12/08, with respect to claim objection to claims 64-66 have been fully considered and are persuasive. The claim objection has been withdrawn.

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Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55-57 and 66 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as stated in the office action dated 7/24/08 and as reiterated below. Response to applicant's arguments appears at the end of the reiterated rejection.

Claims recite a limitation "a variant, derivative and/or a fragment thereof" of peptide of claim 55. It is unclear from the recitation of the claim the nature of "variant", the nature of "derivative" and the nature of "fragment" of the peptide of claim 55. If it is a variant of peptide of claim 55, the claim as recited and the specification as disclosed does not adequately support the claim because, it does not specifically define the nature of variant, whether it is addition, substitution or deletion of amino acids. And if the variant of the peptide corresponds to addition, substitution or deletion of amino acids, neither the claims nor the specification discloses which amino acid in the peptide is being substitute or deleted or added to realize the variability. With respect to defining "variant", the instant specification has the following broad definition on page 18 and paragraph 1, "[I]n particular, variants of the peptide in SEQ ID NO:2, may be defined as those peptides that contain amino acid substitutions, wherein an amino acid can be replaced with another amino acid without altering the activity of the peptide. These amino acids may or may not be conserved across species and may or may not be essential to the activity inhibitory

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function of peptide”. The specification does not clearly specifies which amino acids residues in the parent sequence are substituted.

With respect to derivatives the claims as recited and specification as disclosed does not provide any support to substantiate the invention in terms of the nature of modifications performed on the peptide to obtain the derivatized peptide.

With respect to “fragments”, neither the claims as recited nor the specification as disclosed provide adequate support as to the size of the fragments claimed in the invention and position of the amino acids in the parent sequence corresponding to the fragments. Hence, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Response to Arguments

Applicants argue that the terms such as ‘derivatives, variant and/or fragments’ in claims 55-57 and 66 are well supported and defined in the specification in paragraph 0066-0067. Applicants argue that one of ordinary skill in the art reading the specification as disclosed in the aforementioned paragraphs would know what the terms ‘derivatives, variant and/or fragments’ means. Applicant’s further state that the paragraph 0067 provide that “non-limiting examples of a variant, derivative or a fragment of SEQ ID No: 2 are the amino acid sequences SEQ ID NOs:3 to 13”, as definition for the terms. Thus, adequate support is provided for the terms ‘variant, derivative and fragment’ in the specification and as such the claims point out the subject matter which Applicants regard as the invention.

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Applicant's arguments filed 12/12/08 have been fully considered but they are not persuasive. This is not persuasive because, Section 2106 of the MPEP states that, "Limitations appearing in the specification but not recited in the claim should not be read into the claim" Further, "claims must be interpreted "in view of the specification" without importing limitations from the specification into the claims unnecessarily". According to applicants arguments presented above, applicants state that the SEQ ID NO: 3-13 represents the fragments of the SEQ ID NO: 2. According to applicant's arguments, this limitation appears to be essential subject matter. However, these limitations are not recited in the claims to provide definiteness to the claim. As stated above limitations disclosed in the specification should be read into the claims. The claims as presented also recite derivatives and variants of the peptides. These terms have not been either defined in the claims nor the specification as disclosed provide adequate support to the claims as recited. Hence the rejection under 35 USC 112, 2nd paragraph is proper and is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-59, 61-67 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as stated in the office action dated 7/24/08 and as reiterated below. Response to applicant's arguments appears at the end of the reiterated rejection. The claim(s) contains subject matter which was not described in the specification in

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such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant invention, applicants claim an isolated peptide comprising the amino acid sequence of SEQ ID NO: 2 or a variant, a derivative and/or fragment thereof having the function of reducing the level of serum cholesterol.

Claims 55-58 and 66 recite that the isolated peptide comprises of amino acid sequence of SEQ ID NO: 2 or a variant, derivative and/or a fragment thereof. By reciting that the peptide comprises of SEQ ID NO: 2, applicants are claiming a polypeptide of unknown sequence and unknown length that comprises of SEQ ID NO: 2. In incorporating the limitation that the peptide comprises of amino acid sequence of SEQ ID NO: 2 or a variant, derivative and/or a fragment thereof, applicants are claiming a innumerable polypeptides of unknown sequence composition and unknown structural features. Because, the specification as disclosed does not provide adequate support to claims as recited commensurate with the scope of the claims.

The MPEP clearly states that the purpose of the written description is to ensure that the inventor had possession of invention as of the filing date of the application, of the subject matter later claimed by him. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997). The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include, “level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or

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coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed invention is sufficient” MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated: “A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The specification as disclosed provides a very broad definition for variant as, “[I]n particular, variants of the peptide in SEQ ID NO:2, may be defined as those peptides that contain amino acid substitutions, wherein an amino acid can be replaced with another amino acid without altering the activity of the peptide. These amino acids may or may not be conserved across species and may or may not be essential to the activity inhibitory function of peptide”. The provided definition does not specify the number or location of the substitutions in the

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claimed peptide. The specification also does not provide specific examples of sequences that are representative of variants of SEQ ID NO: 2.

With respect to 'fragments' of SEQ ID NO: 2, the instant claim 56 recites 11 sequences that are fragments of SEQ ID NO: 2 and specification in Table 2 on page 35 discloses 9 peptides. However, neither the specification nor the claims as recited limits the size of the fragments claimed in the instant invention.

With respect to derivatives, the specification only provides a very generic definition such as "[I]n particular, the present: invention provides polypeptides or variants, derivatives and/or fragments thereof having the function of HMGCoA reductase inhibitors, phosphomevalonate inhibitors, reducing the accumulation of cholesterol in the cholesterol biosynthesis pathway and/or reducing the level of serum cholesterol". Thus the specification does not provide an adequate definition in terms of structural features associated with derivatives of SEQ ID NO: 2 encompassed by the claims.

However, the prior art reference of Zhu, et al., 2002, Comparative Biochemistry and Physiology, Part B 131, 749-756 discloses specific peptide sequences that they have characterized derived from molecular cloning techniques belonging to *Buthus martensii* Karsch.

The reference of Torres-Larios, 2000, Eur. J. Biochem., 267, 5023-5031 provides isolation and characterization of 'Hadruin', an antimicrobial peptide from the venom of scorpion.

The claim 64 recites an isolated peptide in general and identifies the peptide only by its function as the peptide having the function of HMGCoA reductase inhibitor, phosphomevalonate inhibitor, reducing the accumulation of cholesterol in the cholesterol biosynthesis pathway and/or reducing the level of serum cholesterol, and wherein the peptide has a molecular weight

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of 16803 Da, 16790 Da, 16791 Da or 17211 Da. By merely providing the molecular weight of the peptides as representative species does not provide adequate written description support to the claims as recited and it does not provide the information about the amino acid sequences representing the peptides. Moreover, the peptide sequence of SEQ ID NO: 2 is a 94 amino acid residue. If the average molecular weight of a naturally occurring amino acid is ~110d for calculating the molecular weight of the polypeptide, the molecular weight of the 94 amino acid residue would be ~10,890d. The molecular weight of 16803 Da, 16790 Da, 16791 Da or 17211 Da claimed for the instant poly peptides represents a ~40% higher molecular weight compared to SEQ ID NO: 2. The other peptides recited in claims 56 and 57 are shorter than SEQ ID NO: 2. It is unclear from the above analysis the true composition of the polypeptide claimed in the instant invention given the fact that there is a ~40% discrepancy in the actual molecular weight of SEQ ID NO: 2 and the molecular weights claimed for the peptides.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is “not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.” MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although, the MPEP does not define what constitute a sufficient number of representatives, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court

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determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

Thus, the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Response to Arguments

1. Applicants argue that for the purpose of advancing prosecution, the currently amended claims 55 and 66 recite ‘An isolated peptide consisting of the amino acid sequence of SEQ ID NO:2, or a variant, derivative and/or fragment thereof...’. Applicants again state that the instant specification, especially from the disclosure on page 18, one of ordinary skill in the art would immediately know the meanings of “variant, derivatives and/or fragments thereof” of SEQ ID NO: 2.

2. With regards to claim 64, applicants argue that the originally filed disclosure in paragraphs 007 and 0131 have the molecular weight for the proteins recited in the claims and provide adequate written description. With regards to the molecular weight of the proteins 40% higher compared to the molecular weight of SEQ ID NO:2, applicants state that ‘interestingly’ the mass of 16kDa protein does not correlate to the mass (of protein) deduced from cDNA (emphasis added by office). Further applicants state that “as mentioned in paragraphs 0069 and 0071, homologs can be obtained from venom of any known species and examples are provided of homologs obtained from the same venom of *Buthus martensii* Karsch and showing inhibition on HMGCoA reductase activity, inhibition of phosphomevalonate, reduction in the accumulation

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of cholesterol in the cholesterol biosynthesis pathway and/or reduction in the level of serum cholesterol, including 16790 Da (JC1-PI); 16791Da (JC2-PI) and 17211Da (JC3- P5). These homologs have similar molecular weights as native JCH2. There thus is no discrepancy between the actual molecular weight of SEQ ID NO:2 and the molecular weight claimed for the peptides”.

Applicant's arguments filed 12/12/08 have been fully considered but they are not persuasive.

1. Though, applicants have amended claims 55 and 66 to recite the peptide using the transitional phrase “consisting of” the claim as recited with the terms “variant, derivative and/or fragments thereof” allows innumerable modifications to the peptide of SEQ ID NO: 2 and is not recited in the limited terms as it intended to be by using the phrase “consisting of”. Although the term ‘fragments thereof’ is defined in the instant specification to be SEQ ID NOs: 2-13, the claims does not recite the limitation. Moreover, as mentioned earlier, Section 2106 of the MPEP states that, “Limitations appearing in the specification but not recited in the claim should not be read into the claim” Further, “claims must be interpreted “in view of the specification” without importing limitations from the specification into the claims unnecessarily”. Therefore, critical limitations can be imported into the claims for interpretation of claims from the specification to provide written description.

2. With respect to applicant’s argument that the original filed specification discloses the molecular weight of the proteins to be 16 kDa and there is lack of correlation between the protein

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obtained by the applicants during isolation process from the venom and the protein derived from the cDNA via molecular cloning methods clearly indicates that the instantly claimed protein of SEQ ID NO: 2 and the proteins isolated from venom are not the same. Moreover, the fact that there is a discrepancy exists between the proteins derived or isolated form from different methods clearly establishes that the proteins claimed in claim 55 is different from that is claimed in claim 65. Additionally, the molecular weight of proteins derived form mass spectral analysis only provides a physical characteristic of the protein. It does not provide the amino acid composition or additional modification of the proteins that exist on the protein such a glycosylation, etc. Hence, applicant's argument that recitation of molecular weight of the isolated protein in the claim provides written description is misplaced. Section 2163 of the MPEP states that "[T]he claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 55-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Possini, et al., 2000, Biochimie, 82, 861-868 as stated in the office action dated 7/24/08 and as reiterated below.

Response to applicant's arguments appears at the end of the reiterated rejection.

In the instant invention, applicants claim an isolated peptide comprising the amino acid sequence of SEQ ID NO: 2 or a variant, a derivative and/or fragment thereof having the function of reducing the level of serum cholesterol.

The reference of Possini discloses the following peptide toxin PiL (Fig. 1, page 863):

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sp      toxin
          10      20      30      40      50      60      70
#1 (1) PiL  -----LVKRG-----TSDGKFEQQT-G-GRNKKI-----RNRKCYG-

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The PiL peptide toxin comprises the tripeptide sequence –CQQ– between the amino acid residues 40 and 50 that corresponds amino acid residues 37-39, a ‘fragment’ of the elected species SEQ ID NO: 3. Since the reference discloses the peptide fragment that corresponds to the instant peptide SEQ ID NO: 3, it is inherent that the peptide exhibit the function of reducing the level of serum cholesterol. The reference also states that the peptides are directly isolated or deduced from nucleotide sequences (page 861, column 2, Material and Methods section). This reads on claims 55-57. The reference also discloses the peptide is isolated from scorpion venom and hence reads on claims 58 and 59.

Hence, the reference of Possini anticipates instant invention.

Response to Arguments

Applicants argue that Possini does not disclose an isolated three amino acid peptide having the sequence of a three amino acid fragment of SEQ ID NO: 3 and three amino acid sequence is described as a part of longer sequence. Applicants also argue that the claims 56 and 57 require that the peptide claimed comprises the amino acid sequences of any of SEQ ID NO: 3-13 and none of which corresponds to the PIL sequence or the three amino acid sub-fragment highlighted by the office.

Applicant's arguments filed 12/12/08 have been fully considered but they are not persuasive.

Although, the instant claim 55 is currently amended to recite “an isolated peptide consisting of”, to define the peptide, the claim as presented recite variant, derivative and/or fragments thereof. The tripeptide of CQQ is a fragment of instant SEQ ID NO: 2 and is also a fragment of instant SEQ ID NO: 3. The terms variant and derivatives recited in the claims have neither been defined in the claim nor has proper definition in the instant specification. Hence, the tripeptide CQQ comprising peptide of Possini reads on the instant claims that recites derivative, variant and/or fragments thereof. Moreover, the claim 57 recites “where the peptide is a fused peptide and comprises at least one peptide, or fragment thereof” in the claim.

Hence the rejection under 35 USC 102(b) as being anticipated by Possini is proper and maintained.

2. Claims 55-60, 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhu, et al., 2002, Comparative Biochemistry and Physiology, Part B 131, 749-756 as stated in the office

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action dated 7/24/08 and as reiterated below. Response to applicant's arguments appears at the end of the reiterated rejection.

In the instant invention, applicants claim an isolated peptide comprising the amino acid sequence of SEQ ID NO: 2 or a variant, a derivative and/or fragment thereof having the function of reducing the level of serum cholesterol.

The reference of Zhu discloses the elected species of the peptide SEQ ID NO: 3 in figure 1, panel B, corresponding to amino acid residues from 23-94. Zhu discloses that the peptide from the cDNA library prepared from venom glands of *Buthus martensii* Karsch scorpions (abstract) using molecular cloning techniques (page 750, column 1, paragraph 1). This reads on instant claims 55-60 and 63. Since the cited reference of Zhu discloses the polypeptide of SEQ ID NO: 3, it is inherent that the peptide exhibits the function of reducing the level of serum cholesterol.

Thus the reference of Zhu anticipates the instant invention.

Response to Arguments

Applicants argue that Zhu had only the nucleotide sequence encoding the peptide and deduced the amino acid sequence from that. In other words, applicants are implying that Zhu did not isolated or synthesized the peptide. Applicants further state that the isolated peptide has a secondary structure different from the predicted by Zhu and an activity different from that suggested by Zhu.

Applicant's arguments filed 12/12/08 have been fully considered but they are not persuasive.

It has been previously illustrated that Zhu characterized the peptides of *Buthus martensii* using the molecular cloning techniques (page 750, column 1, paragraph 1) implying that the peptides were synthesized and isolated by molecular biology (cloning) techniques.

With regards to applicants comment that the secondary structure of the peptide of Zhu was different from that of the isolated peptide, it should be noted that the instant claims are drawn to a peptide sequence of SEQ ID NO: 2 and SEQ ID NO: 3-13, derivatives, variants, fused peptides and/or fragments thereof and not drawn to the secondary structure of a peptide or a protein. According to the information available on the website:

“<http://staff.jccc.net/PDECELL/biochemistry/protstruc.html>”, it is a well understood scientific fact that the secondary structure of a peptide or protein is primarily dependent on the primary structure, i.e., the amino acid sequence composition of the peptide or protein. The website clearly states that, “[P]roteins have a complex three dimensional structure which is important because the function of a protein is closely tied to its three dimensional structure. This nature of this structure is usually explained in terms of a structural hierarchy, from primary to quaternary”. Although, the cited website reference is not a prior art reference in terms of its publication date, MPEP section 2123 states that, “[I]n certain circumstances, references cited to show a universal fact need not be available as prior art before applicant’s filing date. In re Wilson, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include the characteristics and properties of a material or a scientific truism”. Hence the primary structure of the peptide that determines the secondary structure and Zhu discloses that primary structure of the peptide (SEQ ID NO: 2) that the applicants are claiming as their invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 61 and 66-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu, et al., 2002, Comparative Biochemistry and Physiology, Part B 131, 749-756 as applied to claims 55-60, 63 above, and further in view of Torres-Larios, 2000, Eur. J. Biochem., 267, 5023-5031 as stated in the office action dated 7/24/08 and as reiterated below. Response to applicant's arguments appears at the end of the reiterated rejection.

In the instant invention, applicants claim an isolated peptide comprising the amino acid sequence of SEQ ID NO: 2 or a variant, a derivative and/or fragment thereof having the function of reducing the level of serum cholesterol.

The reference of Zhu discloses the elected species of the peptide SEQ ID NO: 3 in figure 1, panel B, corresponding to amino acid residues from 23-94. Zhu discloses that the peptide from

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the cDNA library prepared from venom glands of *Buthus martensii* Karsch scorpions (abstract) using molecular cloning techniques (page 750, column 1, paragraph 1). This reads on instant claims 55-60 and 63. Since the cited reference of Zhu discloses the polypeptide of SEQ ID NO: 3, it is inherent that the peptide exhibits the function of reducing the level of serum cholesterol.

The reference of Zhu does not teach the method steps used in the isolation of the peptide from the scorpion venom.

The reference of Torres-Larios teaches the method of isolating the peptides from scorpion venom particularly 'Hadruin' an antimicrobial peptide from the venom of scorpion *Hadrurus aztecus* (page 5023, column 2, 'experimental section', and page 5024, column 1, 'purification of the peptide section'). The method described includes extraction of the venom and isolation of the peptide by gel filtration and HPLC column chromatography techniques. This reads on the instant claim 61. The reference also teaches synthesis of the polypeptide by chemical synthesis (page 5024, column 1, paragraph 4). The reference also teaches that the peptides were dissolved in 50 mM phosphate buffer, pH 8.0 for enzyme digestion studies (page 5024, column 1, paragraph 2). Since the peptide was dissolved in the phosphate buffer, it meets the limitations of instant claims 66 and 67. Since the peptide is present in the pharmaceutically acceptable composition, it is suitable for oral administration.

It would have been obvious to one skilled in the art to combine the teachings of Zhu and Torres-Larios to arrive at the instant invention. Zhu disclosed the source and the peptide sequence of the instant invention, i.e., SEQ ID NO: 3. Torres-Larios taught how a peptide can be isolated and purified from Scorpion venom for pharmaceutical compositions as described above. One would have been motivated to do so given the fact that Torres-Larios provided a stepwise

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method of extracting the peptide from scorpion venom for pharmaceutical applications. There would have been a reasonable expectation given the knowledge that Torres-Larios successfully purified the peptide from the scorpion venom (from species *Hadrurus aztecus*) and the same could be applied to the instant peptide from the species *Buthus martensii* Karsch.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

1. Applicants argue that “[A]pplicants submit that combining the teachings of the two references would not result in obtaining the isolated peptide of claim 55. Claim 61 has been amended to include that following gel filtration, at least one fraction is selected that has HMGCoA reductase inhibition and then reverse phase HPLC is performed on that fraction. The peptide of the present application has the function of HMGCoA reductase inhibitor, reducing the accumulation of cholesterol in the cholesterol biosynthesis pathway and/or reducing the level of serum cholesterol”. Applicants further argue that the method of isolation of peptides from the

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venom as taught by Torre-Larios would not have been adopted by the person of skill in the art as the two peptides exhibited different functional characteristics.

2. Further applicants argue that “[I]n contrast, Zhu et al. suggest that the peptide of Figure 1(b) is a sodium ion channel toxin. They taught in Section 3.3 of their paper that what they called the BmTXLP2 protein has 78 amino acid residues containing 8 Cys residues forming 4 disulphide bonds, a deduction based simply on direct translation of the nucleotide sequence, and they used bioinformatics to predict that the protein is a sodium ion channel toxin”.

Applicant's arguments filed 12/12/08 have been fully considered but they are not persuasive.

1. Applicants argument that amendment to instant claim 61 that requires a step of selecting at least one fraction with HMGCoA reductase inhibition that is not taught in either of the prior art reference would make it non-obvious is not persuasive. One of ordinary skill in the art who performs a gel filtration column chromatography to separate different molecules based on the molecular size of the compounds to be fractionated would collect different fractions and look for the desired activity. It is obvious to one of ordinary skill in the art that further purification of the fraction may be necessary using other analytical (purification) methods such as reverse-phase. This has been taught in Torres-Larios. Moreover, the instant claims are drawn to the peptide of SEQ ID NO: 2 (product claim). The peptide is disclosed by Zhu. By incorporating the steps of purification into product claim, applicants are rendering the instant claim 61 into a product by process claim. The fact that Zhu discloses the characterization of the SEQ ID NO: 2 by molecular cloning techniques reads on the instant claims as illustrated in the rejection set forth

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above. Again, Torres-Larios teaches a method of purifying and isolating peptides from Scorpion venom. Despite the differences in the functional aspects of the peptides being purified, one of ordinary skill in the art would adopt the method to purify the peptides. The biological activities of the peptides are determined after the purification steps and not prior to it.

2. Applicant's argument that the peptide of Zhu is a 78 amino acid peptide and not a 94 amino acid residue peptide as the instant SEQ ID NO: 2 is not persuasive. In section 3.1 (page 750, column 2) of Zhu teaches that the peptide BmTXPL2 is a 94 amino acid peptide. However, upon cleavage of the signal peptide which corresponds to 16 residues (N-terminal residues), the resulting peptide would be a 78 amino acid peptide ($94-16=78$). The section further teaches that the signal peptide could be 22 amino acids long which would result in a peptide of 72 residues ($94-22=72$). The 72 amino acid peptide corresponds to the instantly SEQ ID NO: 3.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The amendments made to the instant claims 55-57, 59, 61 and 66 does not overcome the previously made rejections in the office action dated 7/24/08.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
Primary Examiner, Art Unit 1654